Annals of Medical Research
DOI: 10.5455/jtomc.2018.01.019 2018;25(3)318-22

Original Article

May ischemia modified albumin be a predictor in diagnosis of contrast induced nephropathy?

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Abstract

Aim: "Ischemia modified albumin" (IMA) was investigated as a possible biomarker in several diseases such as vascular disorders. We aimed to reveal the possible value of IMA in predicting the development of contrast induced nephropathy (CIN) after coronary angiography in patients with stable angina pectoris.

Material and Methods: 106 patients underwent coronary angiography with a diagnosis of stable angina pectoris were included in our study. Basic demographic and clinical findings and laboratory values were recorded and analyzed. Serum creatinine (SCre) levels were also measured 48 hours after coronary angiography and recorded. Amount of contrast agent (CA) given during coronary angiography was recorded. The patients were divided into 2 groups: CIN positive and CIN negative groups.

Results: CIN was developed in 14 patients (13%); and IMA levels were similar in CIN positive and negative groups (p>0.05). SCre (both measurements before and after CA administration) was not correlated with IMA levels. There was no association between drug usage and development of CIN (p>0.05). Comorbidities were not associated with the development of CIN (p>0.05) with the exception of hypertension (HT). Presence of hypertension (p=0.0393) and female gender (p=0.0199) was associated with development of CIN. Mean age was 61.3 and 52.3 in CIN positive and negative groups, respectively (p>0.05).

Conclusion: Any specific biomarker indicating CIN is not available yet. Most frequently used marker is the measurement of SCre 24-48 hours after administration of CA. We found IMA levels not to be a predictor for the development of CIN. Further investigations will clearly determine the importance of IMA as a biomarker in renal failure developed after CA administration.

Keywords: IMA; Contrast Induced Nephropathy; Ischemia Modified Albumin.

INTRODUCTION

Contrast induced nephropathy (CIN) may be defined as decrease in renal functions evaluated as 0.5 mg/dL increase in serum creatinine (SCre) level or 25% increase in basal serum creatinine within 48-72 hours of intravenous contrast agent (CA) administration, independent of presence of clinical signs, symptoms or need of dialysis (1,2). To diagnose as CIN, renal dysfunction should be acute and detected within 2-3 days of CA exposure, and it should not be led by any other potential mechanisms of renal failure (RF). SCre begins to increase within 24 hours of CA exposure, peaks in 3-5 days and then decreases to basal levels within approximately 14 days (2-4). The most important and basic factor contributing to the pathogenesis of CIN is renal ischemia. Several potential risk factors, such as diabetes mellitus (DM), congestive heart failure (CHF), peripheral artery disease (PAD), may contribute to occurrence of CIN (2,4-7). However, preexisting RF is the most important one (8) (Table 1). Sufficient intravenous hydration before and after CA exposure, and preference of low osmolality CA at minimum dose as possible are the basic preventive methods against emergence of CIN (9-11).

CIN contribute to morbidity and mortality significantly; and in some patients it may culminate in chronic renal failure (CRF) (12-15). Therefore, several biomarkers have been investigated as potential predictors of CIN (16-18), and ischemia modified albumin (IMA) is one of them. Hypoxia,

Received: 26.01.2018 **Accepted:** 26.04.2018 **Available online:** 08.05.2018
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acidosis and free radical damage caused by ischemia lead to decreased binding of transition metals, such as cobalt, copper, to N-terminal of albumin. Hence, resulting albumin molecule is termed as IMA (19,20). IMA has been investigated as a biomarker in predicting myocardial infarction (MI) or ischemia, pulmonary embolism, cerebral ischemia, and oxidative stress without ischemia (20-23).

Based on similar physiopathological mechanisms developed in CIN, it may be proposed that IMA could have a role in predicting CIN. We aimed to reveal the possible value of IMA in predicting the development of CIN after coronary angiography in patients with stable angina pectoris.

Table 1. Risk factors for CIN

Absolute risk factors	Potential risk factors	Nonabsolute risk factors
DM and preexisting RF	Hypertension	AIDS
CRF	Nephrotoxic agents	Hypoxia
High osmolality, high dose CA	DM with preserved renal functions	Obesity
Dehydration	Liver dysfunction	Low serum albumin
Decreased intravascular volume	Multiple myeloma	
CHF stage III-IV	Nephrotic syndrome	
Cardiogenic shock and hypotension	Hyperlipidemia	
	Advanced age	
	Solitary kidney	
	Acute MI	
	History of MI	
	Renal transplant patients	
	Hyperuricemia	
	Renal artery disease, PAD	

MATERIAL and METHODS

One hundred six patients underwent coronary angiography in Tepecik Training and Research Hospital between June and December 2014 with a diagnosis of stable angina pectoris were included in our study. Adult patients undergoing coronary angiography with a diagnosis of stable angina pectoris were included. Patients with unstable angina pectoris or acute MI were excluded. We also excluded the patients having inflammatory bowel disease, Behçet's disease, psoriasis, polycyctic ovarian syndrome or chronic liver disease. The patients having other chronic diseases were defined in the results section.

Basic demographic and clinical findings of the patients were recorded. Basic hematologic and biochemical serum values and urinary albumin excretion measured before angiography were recorded. SCre levels were also measured 48 hours after coronary angiography and recorded. Glomerular filtration rate (GFR) was calculated by Cockcroft-Gault formula. Amount of CA given during coronary angiography was recorded.

The patients were divided into 2 groups: CIN positive group (the patients developing CIN), CIN negative group (the patients not developing CIN). CIN was diagnosed as mentioned before. IMA levels were measured in all patients shortly after coronary angiography. Blood drawn for the measurement of IMA was taken into gel tube. After centrifugation, samples were preserved at -80 degree of Celcius. Samples were sent to the laboratory using cold chain procedure. Serum IMA levels were measured by spectrophotometric method as defined by Bar-Or et al (20).

To measure IMA, 200 µL patient serum sample was mixed with 50 µL cobalt chloride and incubated for 10 minutes. After incubation, 50 µL dithiothreitol (DTT) was added, and DTT caused a colored complex with cobalt unconnected to albumin. 1 mL serum physiologic was added 2 minutes later to finish the reaction. Colored complex was measured by spectrophotometric method at wave length of 470 nm. Results obtained after resetting against the sample without DTT were given as absorbance unit (ABSU).

SPSS (Statistical Package for Social Sciences) for Windows 18.0 program was used for analysis. Descriptive findings were defined as mean and standard deviation. When comparing quantitative data, student t test was used for normally distributed parameters, Mann-Whitney U test for parameters not normally distributed. In comparison of qualitative data, Chi-square and Fisher Exact Chi-square tests were used. Results were evaluated with 95% confidence interval and at a significance level of $p<0.05$. Ethical approval was taken by İzmir Tepecik Training and Research Hospital Ethics Committee.

RESULTS

Of all patients (n=106), %58.5(n=62) was male. CIN was developed in 14 patients (13%). Baseline characteristics of the patients were given in Table 2.

IMA levels were similar in CIN positive and negative groups ($p>0.05$) (Table 3).

Mean age was similar in both groups. Serum urea and creatinine levels were not correlated with IMA levels, for both measurements before and after CA administration.

There was no association between drug usage and development of CIN ($p>0.05$) (Table 4). Comorbidities were not associated with the development of CIN ($p>0.05$) with the exception of hypertension (HT) (Table 5).

Table 2 Baseline characteristics of the patients

	Patient groups		p value
	CIN(+)	CIN(-)	
Gender (male/female)	4/10	58/34	0.0199
	Median (minimum-maximum)		
Age	62.5(48-72)	59(42-74)	0.306
Basal SCre (mg/dL)	1.1(0.7-2)	1(0.7-2)	0.92
Basal urea (mg/dL)	38(20-113)	35(4-109)	0.136
SCre at 48th hours	1.55(0.9-3.6)	1.1(0.6-2.1)	0.002
Urea at 48th hours	68.5(33-140)	38(19-118)	0.00

Table 3. IMA levels in CIN positive and negative groups

	mean IMA (ABSU) (minimum – maximum)	p
CIN positive	588 (368 – 798)	0,10
CIN negative	532 (270 – 754)	

Table 4. Drug usage in patient groups

Drug	n		p
	CIN (+)	CIN(-)	
Analgesic	1	24	0,1795
Antithrombotic	8	51	1
Beta blocker/Calcium channel blocker	7	47	1
Oral antidiabetic	5	21	0,3242
Levothyroxine or propylthiouracil	3	9	0,1950
Renin angiotensin system blocker	8	40	0,3955
Diuretic	4	11	0,1098

Table 5. Comorbidities in patient groups

Disease	n		p
	CIN(+)	CIN(-)	
DM	8	29	0,1158
HT	12	50	0,0393
CRF	1	5	0,5
Coronary artery disease	5	47	0,3916
PAD	0	5	1
Cerebrovascular disease	0	4	1
Coronary artery bypass graft	0	6	1
Hypothyroidism	2	8	0,6181
Hyperthyroidism	0	3	1

Presence of hypertension (p=0.0393) and female gender (p=0.0199) was associated with development of CIN. Mean age in CIN positive group was 61.3, and 52.3 in CIN negative group; the difference was not significant (p>0.05).

DISCUSSION

CIN was developed in 13% of the patients. IMA levels were similar in CIN positive and negative groups. Serum urea and creatinine levels were not correlated with IMA levels, for both measurements before and after CA administration. Presence of hypertension and female gender was associated with development of CIN.

In several studies, IMA was found significantly higher in ischemic heart disease, deep venous thrombosis, pulmonary embolism, mesentery ischemia, and cerebrovascular disease. However, it was not significantly different in several other diseases (24,25). The importance of IMA on hypoxia and renal effects associated with CA was not well known. Vascular interventions using CA are important causes of acute renal failure in hospitalized patients. Any specific biomarker indicating CIN is not available yet. Most frequently used marker is the measurement of SCre 24-48 hours after administration of CA (26,27). In our study, IMA levels were similar in CIN positive and negative groups. CIN has generally a relatively shorter recovery period comparing to other causes of acute tubular necrosis (few days to few weeks). Tubular necrosis emerged in CIN is less severe than other causes. Decline in glomerular filtration is due to functional changes rather than necrosis (28). These two explanations could explain the finding that IMA levels were not different in CIN positive and negative groups in our study. However, in other studies examining more chronic processes such as diabetic nephropathy, IMA was also associated with nephropathy (29). In one study, no correlations were found between albuminuria and IMA (30). Therefore, we think that not only the chronicity of the process but also all existing cofactors including comorbidities, drugs, vascular risk factors affect the level of IMA.

In some studies, urinary IMA levels were used to assess the renal functions (30). In one study including 50 type 2 diabetic patients, no correlations were found between serum creatinine levels and urinary IMA levels. They also found that there were no correlations between urinary IMA levels and urinary albumin excretion. These findings could be the result of urinary excretion physiology of IMA. Therefore, simultaneous measurement of urinary and serum IMA might be useful.

In our study, comorbidities were not associated with the development of CIN with the exception of HT. In previous studies, CRF and DM were found to be most important predisposing factors for the development of CIN (7). DM itself may cause oxidative stress in several situation and oxidative stress may play a role both in pathogenesis and complications of DM. We would expect that DM was associated with the development of CIN. However, multiple factors in these patients could affect the results. In one study including 60 type 2 diabetic patients and 30 controls, IMA was investigated as a potential marker of vascular injury in diabetic patients (29). They found the highest levels of IMA in diabetic nephropathy and then earlier diabetic nephropathy, diabetes mellitus without nephropathy in decreasing order. They also showed that the patients having DM without nephropathy had higher levels of IMA than healthy controls. These findings suggested that IMA could be associated with oxidative injury even in diabetic patients without nephropathy. Additionally, IMA levels increased with increasing degrees of diabetic nephropathy. Such a study design including diabetic patients with and without different degrees of diabetic nephropathy, without other acute or chronic complications, exposing or not contrast media would clearly reveal the possible associations between IMA, diabetic nephropathy and contrast media. However, selection of such an isolated sample will be so difficult.

Again, we did not find any association between drug usage and development of CIN. However, in some studies, angiotensin converting enzyme inhibitors were found to

increase the risk of development of CIN (31,32). Female gender was found an important factor to develop CIN in our study. Opposite findings were shown in some studies. Cochran et al. showed that gender was associated with the other factors affecting the development of CIN and males had increased risk (7,33). However, Iakovou et al showed that female patients were at increased risk of developing CIN (34). Increased age was found to be an independent risk factor for CIN in some studies (32). However, in our study, we did not find any differences between CIN positive and negative groups according to age.

CONCLUSION

We found IMA levels not to be a predictor for the development of CIN. As we know, this is the first report indicating the importance of IMA in the development of CIN. However, we did not use regression analyses. It will be clear to reveal the association between IMA and CIN especially in a cohort including patients without any chronic illnesses exposed to contrast media for investigation of arterial disease. We did not evaluate the amount of contrast agent used. The effect of amount of contrast agent used will be revealed by future studies. Further investigations will clearly determine the importance of IMA as a biomarker in renal failure developed after CA administration. IMA would be an important, practical and cheap biomarker in the future.

Competing interests: The authors declare that they have no competing interest.
Financial Disclosure: There are no financial supports.
Ethical approval: Ethical approval was taken by İzmir Tepecik Training and Research Hospital Ethics Committee.

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